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NIH Workshop Report: Taming the Brain's Complexity

Commentary

Robert C. Malenka
Nancy Pritzker Laboratory
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
Palo Alto, California 94304

In the mammalian brain, trillions of neurons are connected by zillions of synapses. This bewildering array of complicated local circuits is influenced by a multitude of diffuse modulatory systems. How in the world are we to make sense of the mind-boggling complexity of the mammalian brain? Clearly, this is a daunting but critically important question, a fact recognized by several NIH institutes (NIDA, NIMH, NINDS) who jointly sponsored a recent workshop (January 2002) to address this topic. A main goal of the meeting was to begin to work out how best to take advantage of the explosion of molecular information and tools now at neuroscientists' disposal. Thousands of genes expressed in the brain have been identified, and we are beginning to map their detailed distributions in specific cells and circuits. We also have rapidly evolving tools that allow the manipulation of genes and their products in the brain with great temporal and spatial precision. The specific workshop tasks included thinking about how best to collect and organize molecular neuroanatomy information so that it is of optimal use to the largest segment of scientists possible. Participants were also asked to think a bit "outside the box" and imagine how current and future molecular technologies might best be used to accelerate our understanding of normal and pathological brain function.

The meeting, ably organized by Marc Tessier-Lavigne and Lubert Stryer with the help of several farsighted NIH program officers, was attended by a distinguished group of neuroscientists, including our most recent American Nobelists, Eric Kandel and Paul Greengard, as well as Sydney Brenner, whose visionary credentials are well established. In addition, there was an appropriate preference for those with molecular orientations and whose technical innovations over the last decade have helped transform the ways we are able to study the brain. Some readers may recognize that the foundation for the workshop was the Brain Molecular Anatomy Project (BMAP), a series of NIH funding initiatives to map genes and gene product expression to specific neuronal cell types so that a Molecular Brain Map can be created (http://trans.nih.gov/bmap).

Like virtually all of the participants, at the end of the two days, I was filled with a mixture of awe and trepidation: awe at both how far we have come and the science-fiction technologies that may be commonly available in the near future; trepidation because of the monumental task facing the neuroscience community as we try to organize, annotate, make accessible, and make sense of the new information and technologies as they become available. A detailed summary of the meeting, including a historical perspective, descriptions of current technologies, efforts, and resources, and specific recommendations with a list of priorities, can be found on the Web (http://trans.nih.gov/bmap/reports/reports.htm). Readers are encouraged to read this document carefully. It provides a wealth of information that may prove invaluable as future research endeavors are planned.

Because the report on the Web provides a comprehensive and eloquent summary of the workshop, here I will briefly mention just a few of the highlights. First, like me, you may not be aware of several existing NIH-funded large-scale efforts to accelerate the development of a Molecular Brain Map. These may already be able to provide you with invaluable tools and resources. At the University of Iowa, Dr. Bento Soares is attempting to identify all transcripts (cDNAs/ESTs) in the developing and adult mouse brain and has so far identified over 30,000 novel ESTs (http://brainEST.eng.uiowa.edu; http://trans.nih.gov/bmap/resources/resources.htm). This will prove invaluable, not only in its own right, but also for the other approaches listed below. Two different gene expression mapping efforts are taking place under the auspices of NINDS's GenSat (high-throughput analysis of gene expression patterns in the CNS) project. At Baylor (and the Max Planck Institute), Dr. Gregor Eichle is mapping gene expression patterns in adult and embryonic brain, using high-throughput in situ hybridization. The goal is to map over 1000 genes per year, an ambitious but achievable task. As an electrophysiologist, an effort that I found particularly exciting is being led by Drs. Nat Heintz, Mary-Beth Hatten, and Alex Joyner (Rockefeller University, New York University) and involves the generation of transgenic mice expressing bacterial artificial chromosomes (BAC transgenic mice) (Heintz, 2001). Because BACs allow very large DNA constructs to be expressed, transgenes with all of their regulatory regions as well as markers such as GFP can be expressed, resulting in mice in which the marker is expressed in the exact same pattern as the endogenous gene. The potential power of this approach is obvious. Imagine being able to readily identify, in living or fixed tissue, cells expressing a specific subtype of receptor, neurotransmitter, channel, or signaling molecule. Because BAC transgenic technology should allow delivery of any transgene to specified cell populations, one can also imagine expressing genetically encoded activity-sensors: a potential boon for those interested in measuring ensemble neuronal activity in slices or in vivo. Such technology might even be used to permit light-induced activation (see, for example, Zemelman et al., 2002) or stable inactivation (for example, by overexpressing potassium channels) of specific cell populations. The data from both the Rockefeller BAC project and the Baylor in situ project will be made publicly available through a website at NCBI, which will open in October. Finally, several investigators in Southern California (Drs. Arthur Toga, Russell Jacobs, and Larry Swanson) are working hard to create computerized atlases of the mouse and human brains. Such standardized coordinate systems are required scaffolds upon which molecular data (i.e., gene expression patterns), and for that matter, all types of data (e.g., connectional data, immunocytochemical data, etc.), must be mapped.

What priorities were suggested at the end of the work-

shop? It was universally concluded that the generation of a Molecular Brain Map has the potential to revolutionize the study of both normal and diseased brain in a manner analogous to the Human Genome Project. It should not, however, be limited to gene expression patterns but also needs to contain connectivity information about the inputs each neuronal subclass receives and the targets that they contact. This enormous endeavor will benefit from an approach that combines a broad survey of gene expression with a more in-depth, detailed focus on model neural circuits, such as those that occur in the retina, cerebellum, or hippocampus. Of course, it will be key to standardize the acquisition and sharing of data in the Map, and full public access is mandatory. Many additional issues were mentioned which clearly warrant further discussion. How can Molecular Brain Maps be extended to species other than mouse and man? To different developmental stages? To diseased brains? How can proteins as well as mRNAs be mapped?

The final recommendation of the workshop worth mentioning is the emphasis that should be placed on the continued development of tools that permit the delivery of genes to specific neuronal populations. I alluded to the incredible power that such technologies afford in the discussion of BAC transgenic mice. Additional enabling reagents include not only banks of BACs but also banks of full-length transcripts/cDNAs, antibody probes, and short promoter elements that will permit cell type-specific molecular manipulations in primates and other nongenetic species. Such specific expression of transgenes will facilitate mapping neuronal connectivity, especially when genetically encoded tracers that are transported across synapses are routinely available (e.g., DeFalco et al., 2001). When everything is in place and optimized such that the connectivity of any molecularly identified cell across two, three, or four synapses can be rapidly elucidated, the expressed gene profile of the cell can be known following any variety of in vivo experiences, and genetically encoded reporters and modulators of neuronal activity can be expressed in your cells and circuits of choice; imagine the experiments you can perform, the insights about brain function that can be garnered.

I strongly encourage you to check out the websites listed in this article. We may have completed the Decade of the Brain, but we are now beginning the Century of the Brain, and you do not want to be left behind. Find out what resources are already available. Share your findings in the databases that are being or will be set up. Let your opinions be known. What we hope to accomplish is nothing less than a thorough understanding of the most complicated entity in the universe. This will take massive and concerted efforts such as those discussed at this workshop. But what better way to spend one's life and, as a consequence, improve mankind's lot.

Selected Reading

DeFalco, J., Tomishima, M., Liu, H., Zhao, C., Cai, X., Marth, J.D., Enquist, L., and Friedman, J.M. (2001). Science *291*, 2608–2613.

Heintz, N. (2001). Nat. Rev. Neurosci. *2*, 861–870.

Zemelman, B.V., Lee, G.A., Ng, M., and Miesenbock, G. (2002). Neuron *33*, 15–22.